Long-term Outcome of Patients with Persistent Pain Following Root Canal Treatment: The National Dental Practice-Based Research Network

A Thesis
SUBMITTED TO THE FACULTY OF THE
UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

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May, 2018

Acknowledgements

I would never be able to thank enough my family for the selfless support and unconditional love that it has been graciously pouring out on me every day, even from thousands of miles away and no matter how late the hour in their time zone. It is their relentless, abundant and self-sacrificial love that has bestowed me precious education opportunities, comforted, refreshed, inspired and carried me on, and enabled me to get to where I am now.

I would like to express my wholehearted gratitude and appreciation to Dr. Donald Nixdorf who noticed my research interest back when I was a young and inexperienced undergraduate exchange student; who has ever since been unwaveringly committed to my growth and development; who has believed in me when I did not believe in myself; and who has continually encouraged me to dream big.

I am also very thankful to my thesis committee members, Dr. Alan Law and Dr. Ruby Nguyen, who have been very supportive of my research endeavors and always available to provide timely help and a much-needed advice.

I am indebted to all the Division of TMD and Orofacial Pain faculty who, with their invaluable knowledge and expertise, have shaped, directed, taught, and helped me learn how to continue to learn more on my own.

I would not have made it through the residency without constant encouragement, gracious care, and kind words of wisdom and calm of my co-residents and friends, Andres Cervantes, Hunia Bushra, Mayank Shrivastava, and Asha Sude.

Finally, I am grateful for the generosity and trust given to me by the PEO International Peace Scholarship and EducationUSA Opportunity Funds Program, which allowed me to pursue my ambitious dreams and this unique educational experience.

Dedication

I would like to dedicate all my efforts put in this thesis to the One who has been dedicated to me more than I ever could. To the One who has sought me relentlessly and opened my eyes to the marvelous truths, who has loved me perfectly and laid down His crown and life to ransom and adopt me into His family, forgiven my wanderings and gave me far more than I could ever dream about or ask for. I want to give all the glory to the Lord Jesus Christ for any praiseworthy work of mine in this thesis. I hope and pray that it will serve for the good of His beloved creation, help stimulate quality research and improve healthcare, and point to the Source of all knowledge and the ultimate Healer.

Abstract

Introduction: About 10% of patients report persistent pain 6 months after root canal treatment (RCT). Little is known about the longer-term outcomes of such patients, their additional care, or factors associated with chronification of their persistent pain. We aimed to measure the longer-term outcomes of patients found to have persistent pain at 6 months and assess for characteristics that differed among patients whose persistent pain continued at 3-years post-RCT versus those whose pain resolved. Finally, we explored long-term pain outcomes of the available specific diagnoses that had been derived for the persistent pain at 6 months after RCT.

Methods: Forty-five patients previously found to have persistent pain 6 months following RCT from the National Dental Practice Based Research Network were approached for a 3-year follow-up, and 27 participated (60%) in the survey. Frequency of self-reported pain (occurring ≥1day(s) in the past month with an average intensity of ≥1/10), its impact on the ability to carry out daily activities, and additional utilization of healthcare were measured. Differences in patient-, pain-, tooth-, dentist-related characteristics were assessed between those patients who continued to experience persistent pain and those whose pain resolved by the 3-year follow-up. Pain outcomes were also assessed in the light of the specific diagnoses derived for the persistent pain by a board-certified endodontist and an orofacial pain practitioner at 65±41 days (~8 months) post-RCT using the data available from the nested study on patients in Midwest region.

Results: Five (19%) patients met criteria for pain at 3.4 years (range: 3.1-3.9) post-RCT, which was moderate in intensity, occurred for about 3 days in the preceding month, and for only one patient, kept them from usual activities and work. Patients whose persistent pain resolved since 6-month follow-up received similar amounts of additional care within each follow-up time window as those whose pain continued. Yet, cumulatively over the 3 years, 4/5 (80%) patients whose pain continued received dental care with no reduction in

average pain intensity. Longer duration of pre-operative pain and higher intensity and interference of persistent pain at 6 months were found among patients with pain chronification. Specific diagnoses for the persistent pain at 6 months after RCT were available for 15/27 (56%) patients and included odontogenic (6), temporomandibular disorder (TMD) (5), mixed odontogenic-TMD (1), persistent dento-alveolar pain disorder (1), and pain-free by the time of evaluation (2). Ten (77%) out of the 13 examined patients improved over the 3 years regardless of the diagnosis or treatment. Eleven (85%) of them had TMD and/or headache either as co-morbid unrelated diagnoses (6, 46%) or the causes (6, 46%) of the persistent tooth pain.

Conclusions: Chronicity of persistent pain at 3 years post-RCT was infrequent. Most patients improved without additional treatments, and those who received additional care did not necessarily have reduced pain. Our preliminary study indicates that chronification of pain may be associated with characteristics previously identified to be related to chronification of pain. Patients presenting for initial RCT and suffering persistent pain after it might need to be carefully evaluated and managed for various orofacial pain conditions mimicking or co-existing with odontogenic pain to improve short- and long-term treatment outcomes.

Keywords: Endodontics, Patient Outcome Assessment, Observational Study, Health Care Utilization, Quality of Life.

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Introduction

Orofacial pain, in particular tooth pain, is the most common reason for patients to seek dental care (Armfield JM, Steward JF, 2007; Maggirias J, 2002). Root canal treatment (RCT) is effective at addressing odontogenic pain, significantly reducing pain intensity, duration, and related interference (Law et al., 2014). Nevertheless, RCT has been shown to be associated with persistent pain, with frequency of all-cause tooth pain measured at ≥6 months after RCT being estimated by meta-analysis to be 5.4% (Nixdorf et al., 2010a) and by observational studies to be 10.0% at about 6 months (Nixdorf et al., 2016) and 5.0% at 3-5 years post-RCT (Vena et al., 2014). This is significant given that over 16 million initial orthograde RCTs are performed in the United States each year (American Dental Association, 2007).

Predictors for persistent pain 6 months after RCT have been explored and include longer pain duration prior to RCT and less optimism about the outcome of the intervention (Nixdorf et al., 2016). Other factors related to persistent tooth pain following RCT may be associated with the presence of endodontic lesions, residual infection, missed canals, cracks and fractures, or procedural complications, but oftentimes no obvious cause for such pain is identified (Nixdorf et al., 2015). A number of secondary causes for persistent "tooth" pain with no signs of pathosis have been proposed in the literature and include referred myofascial or neuropathic pain, vascular, neurovascular or headache disorders, referred cardiogenic or cervicogenic pain or idiopathic mechanisms (Mattscheck et al., 2016). Neuropathic causes for persistent tooth pain after endodontic treatment have been commonly discussed and referred to as atypical odontalgia (Rees and Harris, 1979), phantom tooth pain (Marbach et al., 1982), post-traumatic dysesthesia (Campbell et al., 1990), persistent dentoalveolar pain (PDAP) (Nixdorf and Moana-Filho, 2011), and peripheral painful traumatic trigeminal neuropathy (Benoliel et al., 2011). However, findings of the recent study - using the same patients in this study - determined that almost a half of the cases of the persistent "tooth" pain 6 months after RCT are of a

nonodontogenic origin, and found temporomandibular disorders (TMD) to be the most common cause for such “tooth” pain (Nixdorf et al., 2015).

Persistent pain degrades quality of life and function of those experiencing it (*Relieving Pain in America*, 2011; Shueb et al., 2015). In addition, the parent observational study revealed that persistent pain 6 months after RCT introduces burden of additional care, which includes retreatments, medical appointments and pain medications (Nixdorf et al., 2016). However, little is known about progression of these patients’ pain or the additional care that they seek in the longer term. A combined retrospective/prospective observational large case series determined 5.0% point prevalence of persistent pain among patients with previous history of primary endodontic therapy 3 to 5 years prior to enrollment (Vena et al., 2014). The follow-up observations were made at a single point in time, authors do not report on how they arrived at the population sample, introducing a possibility of selection bias, do not report pre- and post-treatment pain data, and do not assess management of pain over the years. Therefore, this previous study is limited in its ability to determine the true risk of persistent pain after RCT. About 62% of these patients’ persistent pain was attributed to non-odontogenic causes, but specific diagnoses for such pain were not derived. Therefore, this prospective longitudinal study aimed to analyze whether persistent pain, measured at 6 months after RCT, continue to be present at 3 years post-RCT. Specifically, we followed the patients identified as having persistent pain 6 months after RCT to: measure the frequency of persistent pain outcome at 3 years after RCT, estimate the pain-related burden, assess amount and type of treatments received over the course of 3 years, and explore how characteristics of those of them whose pain improved differed from those whose did not. Finally, we explored long-term pain outcomes of the available specific diagnoses that had been derived for the persistent pain at 6 months after RCT and factors associated with chronification of this persistent pain at 3 years.

Materials and Methods

Population source and inclusion criteria

The source patient sample was a large-scale prospective longitudinal study following patients who received RCT from dentists enrolled in the National Dental Practice-Based Research Network (Gilbert et al., 2013, 2008). Details of the study methods have been published (Nixdorf et al., 2012). In brief, patients aged 19–70 years with a permanent tooth requiring initial orthograde RCT were enrolled. Patients and dentists completed questionnaires immediately before and after endodontic treatment visits. In addition, patient questionnaires were collected one week, three months and six months following treatment (Nixdorf et al., 2012). The primary outcome measure of the parent study was persistent pain at the 6-month study recall (Nixdorf et al., 2016). Persistent pain was coded as present if pain occurred one or more days in the past month and average pain intensity in the past month was rated as one or higher on the Graded Chronic Pain Scale (Von Korff et al., 1992). Additionally, questions were asked concerning pain interference with daily activities and work in the preceding month, as well as any medications taken or additional care received since the last follow-up to manage pain associated with the tooth that was treated with RCT. Patients meeting the criteria for persistent pain at 6 months in the parent study were eligible to enter this nested study. For feasibility reasons, only patients within the Midwest (Minnesota) and South Atlantic (Florida) regions of the network were considered for inclusion and were approached for 3-year follow-up data collection. In addition, clinical evaluation was performed by a board-certified endodontist and a board-certified orofacial pain practitioner for a subset of patients (in Minnesota region) to derive specific diagnoses for persistent pain determined at 6 months after RCT at 65±41 days (~8 months after RCT) after completion of the 6-month questionnaire.

Data collection

Patients completed 3-year questionnaires that collected similar primary outcome data as at the 6-month follow-up with the same criteria used to define persistent pain at 3 years as at 6 months. Additionally, we analyzed previously collected data in the parent study to

compare patient-, pain-, tooth-, dentist-related characteristics, as well as patients' assumptions about the cause for their persistent pain and health-care utilization between those patients who were found to continue experiencing persistent pain since the 6-month follow-up and those whose pain reportedly resolved by the 3-year follow up. These characteristics were compared at each available follow-up time point: pre-operatively, immediate and 1 week post-operatively, 3 months, 6 months, and 3 years post-RCT. Finally, we assessed the pain outcomes in the light of the specific diagnoses derived for the persistent pain at 6 months post-RCT using the data available from the nested study on patients in Midwest region.

Data analysis

Data was recorded on paper forms and entered into an Excel database (Microsoft, Seattle, WA). SAS V9.3 (SAS Institute Inc., Cary, NC) was used for the analysis. Descriptive statistics (the mean, SD, frequencies, proportions, median, range) were used to summarize the data. Wilcoxon rank sum tests were used to compare the distributions between the two groups (patients with and without report of pain at 3-year follow-up) for continuous variables. Fisher's exact tests were used to compare the proportions between the two groups due to very small sample sizes in some of the analysis cells. P-values were not adjusted for multiple comparisons given the small sample size and the exploratory nature of the study.

Results

Frequency of persistent pain 3 years after RCT

Out of 65 patients from the parent study who had persistent pain at 6 months after RCT, 45 were enrolled in the Midwest and South Atlantic regions and thus were considered eligible cases to be followed (Figure 1). Only patients who had consented for extended follow-up were invited to participate in this study. The average time duration since the initial RCT to the long-term follow-up questionnaire was 3.4 years (range: 3.1–3.9; SD = 0.2). Twenty-seven patients provided long-term follow-up data, which comprised 84% of the eligible sample. Five of the 27 patients (19%) who reported persistent pain 6 months after RCT continued to meet criteria for persistent pain at the long-term follow-up.

Baseline patient-, tooth-, pain- and dentist-related characteristics of patients with pain at >3 years after RCT

The following describes the 5 individuals who reported pain 3 years following RCT. The mean age of patients with pain was 46±15 (median 49) years old (Table 1). Most patients were white (80%), female (80%), with dental insurance (80%), income of over $50,000 (100%), and completed college or advanced level education (80%). Average pain intensity was 6/10 (range 3-9/10) with median duration of 7/7 days (range 6-7/7) in the week preceding the RCT. One patient reported chronic tooth pain (present at least 8 hours a day, 15 days or more a month, over the last 3 or more months) and a widespread body pain at baseline. Three (60%) of the patients were very much fearful about the RCT, but all (100%) expected good to very good treatment outcomes. Mandibular teeth comprised 60% of treated teeth, and 100% were posterior teeth. Of the 5 endodontically treated teeth, 80% had an initial diagnosis of symptomatic irreversible pulpitis and 80% had symptomatic apical periodontitis. Three (60%) RCTs were treated by endodontists and 2 (40%) by general practitioners. No procedural complications were reported by the treating dentists and obturation was completed in one appointment in 4 (80%) of the teeth, with 2 (40%) of them receiving a permanent restoration at the same visit. Most of the teeth (60%) showed no signs of periodontal disease with probing pocket depths of ≤3 mm. Two teeth (40%)

had minor periodontal bone loss with maximum probing depths measured to be 4 and 5 mm.

Additional healthcare utilization and pain-related characteristics of patients with pain at >3 years post-RCT measured at 1 week, 3 months and 6 months following the RCT

Mean and median pain intensity decreased from severe pre-operatively to moderate (4/10) a week after RCT; however, remained stable at all subsequent follow-ups (Table 2, Figure 2). Average pain duration dropped by about a half at the first week post-RCT with a less prominent reduction in the pain days at the following survey periods (Table 3). Pain minimally interfered with daily activities across all time points, being slightly more disruptive on a week following RCT (Table 4). Most patients continued taking medications for pain associated with the RCT-treated tooth from baseline to 6-month follow up (Table 5). One patient had occlusal adjustments within the first 3 months after RCT reporting an increase in pain intensity at the follow-ups, and other 2 patients underwent a re-treatment and a tooth extraction in attempt to ameliorate the pain between the 3- and 6-month recalls with no reduction in pain ratings (Table 6, Figure 2).

Health care utilization since determination of persistent pain at the 6-month follow-up

Overall, 11 out of 27 (41%) patients with persistent pain at 6 months continued to seek care for this pain after this 6-month timeframe (Table 7). This included 8 (30%) patients having 14 additional dental visits and 3 appointments with medical doctors, and 7 (26%) patients taking pain medications after the 6-month timeframe. No difference was found between the amount of additional care received after 6-month follow up by patients whose pain persisted or resolved by the >3-year follow-up timepoint. Three patients (60%) who continued experiencing persistent pain had been taking medications for pain ever since the 6-months follow-up time frame. Two (40%) patients with report of pain at >3 years saw their dentist three times each with 1 of them (20%) receiving an additional RCT within the preceding 2 years. Of the 22 (81%) patients who did not meet the pain criteria any longer,

4 (18%) took pain medications, 6 (27%) had 3 medical and 8 dental appointments including 2 additional RCTs, 1 crown replacement, and 1 tooth extraction since the previous follow-up.

Additional care received since the initial RCT up to >3-year follow-up

Overall, from the initial RCT to the >3-year follow up time frame, 11 (41%) patients had 36 dental, 8 medical and 4 chiropractic appointments and 24 (89%) took medications to address pain associated with RCT-treated tooth (Table 6). There was no statistically significant difference in the amount of care received at each follow up between patients with and without long-term persistent pain (Figure 3). However, by the 3-year follow-up, 4/5 (80%) patients who continued to report pain received additional treatments, including 2 re-treatments, 1 extraction and 1 occlusal adjustment. In contrast, only a third (32%) of those who reported persistent pain at 6 months but no longer experienced it at >3 years attended to their pain and received further treatment after the initial RCT (Figure 4). Regardless of these treatments, pain intensity scoring of those with 3-year persistent pain remained almost unchanged across all follow-ups from 1-week post-RCT to the >3-year follow-up (Figure 5) (Table 2).

Pain-related characteristics and its impact on patients with persistent pain at >3 years after RCT

Patients with pain at >3 years reported moderate (4/10) pain intensity with an average of 6 days (median: 3; range: 2-20; SD=7.7) duration in the preceding month. One of these patients (20%) was kept from usual activities for 1 day due to pain, which somewhat (1 on the scale 0-10) interfered with their ability to work (Table 8).

Factors associated with chronification of persistent pain after RCT

Absence of association

No association was found between long-term persistent pain and intensity of pre-operative pain, pulpal/apical diagnoses at baseline, pre-emptive analgesia, dentist's specialty status, intraoperative complications, permanent restoration placement, difficulty or number of appointments to complete the RCT, dentist's expectation of persistent pain at 6 months,

female gender, widespread pain, or patients' optimism about the outcome of the treatment (Tables 2, 9-12).

Presence of association

Factors found to be associated with chronification of persistent pain following RCT included daily or nearly daily (6.8/7 days) duration of pre-operative pain in the week prior to RCT (p=0.0493) as well as reports of moderate (4-6/10) intensity of the persistent pain (p=0.0452), and interference with usual activities at 6 months following RCT (p=0.0395) (Table 3). Extreme fear of RCT was reported by 3/5 (60%) of patients developing long-term persistent pain compared to 3/22 (14%) of patients with no pain at >3 years (unadjusted p=0.537) (Table 9 and Figure 6). Overall, 4/5 (80%) chronic pain patients had additional treatments over the >3-year period compared to 7/22 (32%) patients no longer having pain (p=0.1252) (Table 6).

Clinical differential diagnoses given for the persistent pain at 6-month and their long-term outcomes

Out of 27 patients surveyed at >3 years, 20 (74%), including 3 patients with- and 17 without long-term persistent pain outcome, were from Minnesota. These patients were eligible for clinical evaluation by both board-certified endodontist and orofacial pain practitioners shortly (65±41 days or about 8 months) after determination of their persistent pain at the 6-month follow-up to derive specific diagnoses in the nested study (Nixdorf et al., 2015). Fifteen of these patients who had been assessed and given a consensus diagnosis for the persistent pain at 6-months after RCT happened to be enrolled and represent 56% of the sample in this 3-year outcome study.). Two patients had already been pain-free by the time of clinical evaluation. Ten (77%) out of the 13 examined patients improved over the 3 years regardless of the diagnosis or treatment, and 3 patients still experienced persistent pain at >3 years (Figure 7). The two patients who no longer had pain at the 8-month examination remained pain-free at the 3-year recall. One of them, however, received RCT to address tooth pain that occurred after the clinical assessment.

One (8%) patient had received a diagnosis of PDAP for the persistent “tooth” pain. This patient was also diagnosed with co-morbid TMD and migraine headaches and received endodontic re-treatment prior the study evaluation (between 3-6 months after RCT). This patient’s average achy and throbbing pain remained 6/10 in intensity from pre-operative baseline until 3-year follow-up, flaring-up once at 1-week post-initial RCT.

Five (38%) patients had been diagnosed with TMD as the sole etiology for the persistent pain at >6 months after RCT. One of them, who had been determined to have referred myofascial pain, continued having persistent “tooth” pain at 3 years. This patient did not pursue additional evaluation or treatment over the >3 years. The remaining 4 patients diagnosed as having TMD-related persistent “tooth” pain experienced a resolution of their pain by the >3-year follow-up, with only one of them having consulted a physician for this pain.

Six (46%) patients had been diagnosed with purely odontogenic pain stemming either from the previously treated (3/6) or an adjacent (3/6) tooth. One patient who continued suffering from pain for >3 years had been previously diagnosed with failed RCT (missed MB2 and crack) as the etiology for the persistent pain. The patient also had been diagnosed with comorbid TMD and tension-type headache. This patient subsequently underwent re-treatment with minimal amelioration (from 3/10 to 2/10) of the persistent pain at 3 years. One patient had been given a diagnosis of symptomatic irreversible pulpitis of the adjacent tooth for the persistent pain, for which an endodontic treatment was provided that resolved the persistent pain completely. Interestingly, the remaining 4 patients, in whom odontogenic causes (missed, calcified, C-shaped canals, and cracks) for the persistent pain were determined at 6 months, improved without seeking any additional treatment by >3 years.

One (8%) patient had been determined to have co-presenting TMD and an adjacent tooth pathosis (increased cold sensibility testing and bite tenderness) both contributing to the persistent pain. The patient also had a co-morbid tension-type headache. At the 3-year

questionnaire; however, the patient reported that the pain gradually and completely resolved before the scheduled appointment to address the dental pathosis and thus the treatment was no longer pursued. Overall, 11 (85%) out of 13 examined patients had TMD and/or headache either as co-morbid unrelated diagnoses (6, 46%) or the etiology (6, 46%) of the persistent "tooth" pain. In addition, 9/10 patients without persistent pain at >3 years and 1/3 patients with persistent pain at >3 years reported having other chronic pain conditions.

Patient-perceived cause for the persistent pain

Only a little over a third (10) of all patients responded on each questionnaire about the perceived cause for their persistent pain at 6 months and >3 years. Half of them reported that the RCT was the cause for the persistent pain at 6 months. At 6 months after RCT, 50% attributed their persistent pain to "dental treatment" (*e.g.* RCT), 40% did not know the cause, and 10% presumed "trauma" to be the cause for their pain. Interestingly, at the >3 year follow-up, after the clinical examination by the orofacial pain provider, 40% of patients with persistent pain now responded that "other pains" (headache/TMD) were the reason for their persistent "tooth" pain experience (of these patients, 20% previously reported dental treatment and 10% did not know the cause for the pain), 30% still thought "dental treatment" caused the persistent pain, 10% attributed it to "illness" (cold/sinus/ear infection), 10% to "trauma", and 10% did not know the cause. Fourteen (74%) out of 27 of patients responded to the question about usefulness of the received clinical evaluation by an orofacial pain practitioner. Almost 73% of pain-free patients and 33% of patients with long-term persistent pain perceived significant benefit.

Discussion

Frequency of persistent pain 3 years after RCT

Our findings suggest that chronification of persistent pain after RCT is infrequent, occurring approximately in 1 of 5 patients that have persistent pain at 6 months. Furthermore, persistent pain at 3 years following RCT was found to have minimal impact on daily life but repeated additional treatments were received and did not reduce pain intensity.

Under the assumption that there were no other patients with long-term pain outcome in the entire initial patient pool receiving RCT (708 patients), including in those not able to be followed, the most conservative estimate of prevalence of persistent pain at >3 years after initial non-surgical RCT would be 5/708 or 0.7%. Assuming patients not followed were similar to the ones followed, meaning an additional 4 patients for the 18 not followed would have persistent pain from the 481 patients providing 6-month data in the Midwest and South Atlantic regions, the less conservative estimate of prevalence of persistent pain at >3 years following initial RCT would be (5+4)/481 or 1.9%. Assessing this range of estimates, a simplistic point estimate that can be concluded from this data is that the prevalence of persistent pain >3 years following RCT is 1%.

A broadly inclusive systematic review by Nixdorf et al. (Nixdorf et al., 2010a) identified 26 studies (2,996 enrolled teeth) that reported participants' pain status, regardless of etiology, at 6 months or later after root canal treatment. Across studies, the summary estimate of all-cause persistent pain was 5.3%. The reporting unit was the tooth, whereas the outcome of persistent pain is a patient-based measure. This choice means that one person could have more than one root canal procedure being counted. In addition, the studies were mainly performed in university-based settings or tertiary care centers, likely resulting in an increase in the estimate of unfavorable health care outcomes since more difficult patients tend to be seen in these environments.

Persistent pain prevalence of 5% determined by Vena et al (Vena et al., 2014) at 3-5 years after initial RCT in general and specialist private dental practice is also larger than the frequency estimate in our patient population. The authors used an efficient combined retrospective and cross-sectional study designs and enrolled a large number of patients, with resulting frequency estimate in line with the previous meta-analysis (Nixdorf et al., 2010a). However, the authors do not report on how many patients they contacted and how many of them followed up, potentially introducing selection bias associated with such a convenience sample of patients who have an ongoing relationship with the dental practitioners. In addition, the follow-up observations were made at a single point in time with no reported consideration for the history of the chief complaint, pain presentation or its management over the years, further introducing potential confounders (new onset pain unrelated to RCT, related to re-treatments, etc).

Polycarpou et al (Polycarpou et al., 2005) assessed prevalence of persistent pain 12-59 months after "successful" RCT and estimated it to be 12%. The high number is likely driven by low 44% recall rate and the specific patient population referred to their tertiary care center, compared to our patient population from general and endodontics dental offices. It is also important to mention that the Polycarpou study included cases with periapical surgeries and the vast majority of teeth were re-treated non-surgically. Thus, it is hard to derive conclusions on whether there is an association of the persistent pain outcome with the RCT itself, complications and failure of previous RCT, risks and complications specific to endodontic re-treatments and surgeries, or the patient-related characteristics.

A survey study (Klasser et al., 2011) investigating the prevalence of persistent pain of neuropathic origin after a single tooth nonsurgical root canal treatment in a postgraduate endodontics clinic over a 4-year period using a modified S-LANSS questionnaire found it to be 7%. However, the prevalence was likely overestimated due to a very low response rate of 10.7%, which might explain the significantly higher VAS (7.2/10) scores compared

to our sample. Moreover, modified S-LANSS was found to have inadequate accuracy to detect intraoral neuropathic pain (Herrero Babiloni et al., 2017).

Marbach et al (Marbach et al., 1982) investigated incidence of phantom tooth pain after RCT surveying a specific group of patients treated by a single endodontist. Recall rate for clinical evaluation was only 50% (15/30), no timeframe to follow-up was reported, 10-item questionnaire was used (with no information on repetitive dental procedures), with the authors proposing deafferentation/neuropathic causes for the observed persistent pain. Although 15 patients with persistent pain were clinically examined, the author excluded 4 male patients from the analysis for unknown reasons. The author's conclusions about 3-6% incidence of phantom tooth pain after RCT should therefore be interpreted with caution.

Oshima et al. (Oshima et al., 2009) evaluated patients in a tertiary care center for incidence of specifically neuropathic pain after orthograde and re-RCT and found it to be 5.9%. Again, the higher frequency rate is likely associated with the specifics of the patient sample. Unfortunately, the authors do not report on the incidence of other non-odontogenic causes of pain that they excluded from their analysis.

Characteristics of patients with pain at >3 years after RCT

At baseline, patients who were later found to have continued persistent pain 3 years after RCT were very similar to those with favorable outcome. Most were white female patients with college education, high income and dental insurance, had a diagnosis of symptomatic irreversible pulpitis and symptomatic apical periodontitis, were treated either by an endodontist or a general practitioner none of whom encountered any difficulty performing the treatment either reported any procedural misadventures. When compared with patients who did report persistent pain at 6 months, which subsequently resolved, the patients with chronic pain had nearly daily pain duration in a week preceding the RCT and were more fearful of the upcoming dental procedure. These patients also reported significantly higher (moderate) pain intensity and pain interference with usual activities at 6 months after RCT

compared to those whose pain gradually resolved by the 3-year follow-up. Thus, our data suggests that very few features if any distinguish patients with pain chronification after RCT either at baseline or at follow-up.

Factors associated with chronification of persistent pain after RCT

In the assessment for association of pain at 3 years after RCT, we found that longer pre-treatment pain duration, moderate intensity of persistent pain and its interference with usual activities at 6 months after RCT were associated with pain chronicity, as well as intense fear of RCT (marginal association). Pre-operative pain duration (in all types of dental care and RCTs) has been reported in literature investigating longer term pain as a factor associated with chronic pain (Lewis et al., 2015; Pigg et al., 2013; Polycarpou et al., 2005; Viniol et al., 2015).

Nixdorf et al. (Nixdorf et al., 2016) found that pain duration a week prior to RCT and patient's expectations were predictors for persistent pain at 6 months post RCT. The latter does not seem to be associated with pain chronification in this 3-year analysis, however the nearly daily pain a week before RCT differentiates patients who continue to have pain 3 years later.

On the other hand, Vena et al. (Vena et al., 2014) did not find pre-operative pain duration to be associated with persistent pain, but found that treatment by endodontists correlated with the long-term all-cause persistent pain. Non-odontogenic pain, for which specific diagnoses were not derived, was present in 62% of their patients with persistent pain outcome and was more common in patients previously treated by endodontists. Lack of pre- and post-operative history does not allow speculation about whether such a pain was misdiagnosed pre-RCT, presented as co-morbidity, resulted from the dental procedure or, occurred later due to other causes. The authors also found that patients treated by endodontists had more psychological discomfort, suggesting the greater complexity of such patients, which supports findings of Abbot et al. (Abbott, 1994) who explored reasons for referral to endodontists (complex patients with difficult root canal anatomy and greater

pain experience). However, in our sample, we did not observe correlation of patients' fear/expectations, tooth type or pain intensity with type of dental practitioner performing the treatment.

Polycarpou et al. (Polycarpou et al., 2005) proposed 9 "factors affecting the occurrence of chronic nonodontogenic pain", including female gender, white ethnicity, history of previous chronic pain and painful treatment in the orofacial region, presence and >3 month duration of preoperative pain, pre-operative tooth tenderness, and non-surgical re-treatment. Although, the authors studied a different patient population and surgical RCTs as well as performed multiple comparisons without appropriate correction for such, we found similar characteristics in patients with pain chronification.

Klasser study (Klasser et al., 2011), despite its significant limitations, found some similarity with our findings, specifically no gender preponderance, mean age, predominance of report of pain in the mandibular teeth.

In Oshima study (Oshima et al., 2009), patients with neuropathic pain were predominantly female (13:3), majority (87.5%, 14/16) had maxillary pain, and most patients (62.5%, 10/16) developed pain after undergoing retreatment. These differences with our findings can be explained by the study design and patient source, which were discussed above.

Prevention of chronic pain should include reduction of pre-operative pain duration, which might mean patient education and counselling about the procedure as well as implementations of programs aimed at increasing access to care. In addition, since the intensity of the post-operative and persistent pain at 6 months after RCT was associated with chronification of such pain, early and appropriate diagnosis and management of patients who show signs of persistent post-endodontic pain should be employed.

Additional healthcare utilization

Patients with persistent pain at 6 months after RCT, regardless of their pain outcome at >3 years, continued to equally and extensively utilize health care to address the pain associated with RCT-treated tooth. However, while 4/5 patients with report of pain at >3 years underwent additional treatments with no relief, two thirds of patients no longer experiencing pain at >3 years did not require any additional treatment after the initial RCT for resolution of their persistent pain. It might be appropriate to educate and reassure patients about frequency of persistent pain 6 months and 3 years following RCT and its likelihood to resolve over time without repetitive invasive dental procedures, mentioning however that recovery may take months to years without appropriate care.

Our data is suggestive that the utilized health care likely did not address the cause of the post-RCT pain or perpetuated it. According to a meta-analysis (Nixdorf et al., 2010b), about a half of patients with persistent "tooth" pain suffer from non-odontogenic pain. Based on a recent study (Nixdorf et al., 2015), which is a catchment for this analysis, it would be expected that these chronic pain patients suffered from comorbid or possibly misdiagnosed TMD. This notion is supported by the evidence of high prevalence of TMD in general and dental patient populations (Gillborg et al., n.d.; Goulet et al., 1995; Hongxing et al., 2016; Lövgren et al., 2016; Talaat et al., 2018). While Manfredini et al. (Manfredini et al., 2011) estimated 13% prevalence of masticatory muscle pain in general population, Talaat et al. (Talaat et al., 2018) reported 10.8% prevalence of TMD discovered incidentally during routine dental examination, 17.5% of which was myofascial pain. Nixdorf et al. (Nixdorf et al., 2015) found that 41% of patients with persistent "tooth" pain at about 8 months post-RCT had exclusively TMD as its cause. It might be associated with muscle-guarding and central sensitization of the trigeminal system secondary to dental pain (Sunakawa et al., 1999; Wright and Gullickson, 1996), referred myofascial pain patterns (Wright, 2000), and myofascial pain caused by prolonged mouth opening during dental procedures (Ohrbach et al., 2013; Sahebi et al., 2010). It is also possible that neurovasular pain disorders may have mimicked "tooth" pain in some of these patients (Alonso and Nixdorf, 2006; Czerninsky et al., 1999; Hryvenko et al., 2018; Nixdorf et al., 2008). Some

of these patients' chronic pain might have been of neuropathic origin, and it is expected that in addition to inability to ameliorate the pain with the invasive dental procedures they may cause repetitive nerve injury, perpetuate or even aggravate the pain (Malacarne et al., 2017; Marbach, 1993; Nixdorf and Moana-Filho, 2011; Ram et al., 2009). General dentists and endodontics must be familiar and recognize, or provide an early referral for evaluation of different non-odontogenic sources of "tooth" pain to avoid multiple inappropriate, irreversible, potentially harmful, and costly interventions and pain chronification.

Differential diagnoses for persistent pain at 6 months after RCT and their long-term outcomes

Exploring the dataset of the nested study with differential diagnoses for the persistent pain at 6 months available on over a half of patients in this long-term outcome study, we found that a half of the study patients had had a non-odontogenic cause for their persistent pain. Moreover, 11/13 the examined patients received TMD and/or headache diagnoses whether or not related to the persistent tooth pain. Interestingly, regardless of their diagnosis, most of the patients with persistent pain at 6 months post-RCT seem to have improved by the 3-year time point without treatment. Majority of patients with TMD as the cause of their persistent tooth pain improved over time with minimal additional care; however, 1 out of 5 patients did develop chronic pain. Surprisingly, the majority (4/6) of patients with odontogenic cause for their persistent pain no longer had pain at the 3-year recall without undergoing additional dental treatment. Similarly, the patient with mixed odontogenic-TMD pain recovered before the scheduled treatment.

In turn, the only patient that did not have pain resolution with solely odontogenic pain as a cause for the persistent pain even with the re-treatment happened to have co-morbid orofacial pain diagnoses. This might be suggestive of either the fact that odontogenic pain of symptomatic apical periodontitis can be self-limiting in nature or that, even though the co-morbid TMD and headache did not reproduce the "tooth" pain, they played a greater role in the pain presentation than previously presumed. Further, there is a controversy in literature regarding whether the percussion sensitivity truly represents apical pathosis

suggested by consensus terminology of the American Association of Endodontists ("AAE Consensus Conference Recommended Diagnostic Terminology," 2009), which was used in this study to derive the consensus diagnoses. For example, Marquis et. al in Toronto Study project (Marquis et al., 2006) assessed outcomes of endodontic treatment and classified teeth with slight tenderness to percussion in the absence of pain to biting as "healed", while Fricton (Fricton, 1999) described it as a symptom of non-odontogenic pain, defined as "periodontal ligament sensitivity" secondary to clenching, repetitive trauma, or gross occlusal prematurity.

It is likely that the patient with PDAP did not improve given that the majority of such continuous neuropathic pain conditions tend to remain painful and stable for years. Pigg et al (Pigg et al., 2013) surveyed patients previously diagnosed with atypical odontalgia either after endodontic treatments or dental extractions to assess their long-term outcomes 7 years after the diagnosis. Over the years, pain improved in 35%, remained unchanged in 60% and worsened in 5%. In addition, 70% patients had ongoing treatment for the pain at follow up. Low baseline pain intensity was the only predictor of favorable prognosis. Although the results cannot be compared to those in our study because the data was limited to one diagnosis of the persistent "tooth" pain and the patients did not necessarily receive initial RCT prior to the diagnosis, it shows similar trends with regards to health care utilization and factors associated with pain chronification. In addition, our patient's pain presentation might have also been complicated by the multiple nociceptive inputs of the co-morbid TMD and migraine into the trigeminal system. This patient's pain rating has not changed over time from pre-RCT and across all follow-ups suggesting possible misdiagnosis and an inappropriate RCT in the first place as well as the re-RCT at follow-up. The patient did not seek appropriate care for the neuropathic pain or comorbid conditions after the clinical evaluation and diagnosis, which might have also played a role in pain chronification. Multidisciplinary care to address comorbid pain conditions might be necessary for PDAP and TMD patients to improve short- and long-term outcomes.

Limitations and strengths

A limitation of our exploratory study is that it resulted in a small sample, and so the observed statistical differences might give a false sense of precision. Our patients were drawn from 2 out of 5 geographic regions, with some loss to follow-up, resulting in only 5 patients with long-term pain outcome and, therefore, might not be representative of a population at large. Another limitation is that, although clinical diagnoses for the persistent pain at 6 months after RCT were available for almost a half of the patients, most of the data was obtained from self-reports of pain without clinical examination at >3 years after RCT. Therefore, primarily patients' symptoms of pain, as opposed to specific diagnoses, were studied. Another limitation is that only those patients who reported pain at 6-month follow-up were surveyed, and so it is possible that some who were asymptomatic at that point in time developed persistent pain later on but were not included in this analysis. Finally, because number of observed outcomes were so small, and factors considered to be associated with pain chronification are so numerous, it was not appropriate to use multiple regression analysis to assess for predictors for such long-term pain outcome. Our study was not powered to assess predictors for persistent pain, but rather explored possible associations with pain chronification in order to look for and propose a hypothesis to be tested with new data.

Nevertheless, such a secondary analysis of the existing datasets is a cost-effective and best-available way to gain an understanding of how big the problem of chronic pain after RCT is, to help further the field, and to design studies specifically aiming to assess the long-term outcomes of patients undergoing initial RCT. Another strength of our study is that it a prospective longitudinal study that ranks higher in the hierarchy of evidence than retrospective studies and analyzed data collected at several time intervals minimizing recall bias. In addition, our study is patient-centered and assessed long-term outcomes. Probably, the greatest strength of this study is the richness of our data across multiple data points with patients' input. This helps understand the prognosis of such patients, but comes at the cost of the sample size. Further, we explored association of persistent pain following RCT

with other orofacial pain conditions combining the clinical data available from the nested study.

Future studies investigating chronification of persistent pain following RCT and assessing predictors for these unwanted outcomes should include differential diagnosis for this pain and reasons for recurring care. Given the striking number of patients with orofacial pain conditions either associated, or seemingly unrelated, to the persistent pain after RCT found in our sample, future studies should also explore prevalence and impact of such co-morbidity in patients presenting for RCT to improve patient selection and treatment success.

Conclusions

Three-year follow up on patients with persistent pain at 6 months after root canal treatment suggests that continuation of persistent pain is uncommon, with about 20% still reporting persistent pain at >3 years later. Assessing the frequency of this longer-term outcome from the perspective of when patients initially receive RCT, a simplistic point estimate is that 1% of patients continue to report persistent pain >3 years later. The patients experiencing persistent pain at >3 years reported that it was moderate in intensity but had little impact on daily life. More than a half, that is 15/27 or 56%, of patients with persistent pain at 6 months post-RCT improved without seeking additional interventions. Both the group that improved with pain resolution and the group that continued to experience pain had a mixture of odontogenic and non-odontogenic etiologies underlying their pain, suggesting that there is a need for both perspectives to be included in the diagnosis and management of patients with persistent pain following RCT.

Tables

Table 1. Patient-, tooth-, and baseline pain-related characteristics of patients with persistent pain at >3 years.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Patient-related characteristics					
Age	26	66	49	51	36
Ethnicity	Non-Hispanic	Non-Hispanic	Non-Hispanic	Non-Hispanic	Non-Hispanic
Race	White	White	White	White	Middle Eastern
Gender	F	M	F	F	F
Dental insurance	yes	no	yes	yes	yes
Income	>50,000	>50,000	>50,000	>50,000	>50,000
Education	College	College	College	Some college	College
Tooth-related characteristics					
Tooth #	3	3	29	21	19
Dx (Pulpal)	SIP	SIP	Necrotic pulp	SIP	SIP
Dx (Apical)	SAP	SAP	SAP	Normal	SAP
Perio probing	3mm	5mm	4mm	3mm	3mm
Complete RCT	yes	yes	yes	no	yes
Misadventure	none	none	none	none	none
Restoration	no	yes	yes	no	no
Difficult RCT	no	no	no	no	no
Practitioner-related characteristics					
Specialty	Endo	Endo	GP	GP	Endo
Years in practice	13	20	24	8	X
Baseline (week preceding RCT) pain-related characteristics					
Average pain intensity	7/10	3/10	9/10	6/10	6/10
Pain duration (d)	7/7	7/7	7/7	7/7	6/7
Pain interference with work	no	yes	yes	yes	no
Days with pain interference	0/7	0/7	2/7	2/7	0/7
Pain medications	yes	yes	yes	yes	no
Chronic pain	no	no	yes	no	no
Widespread pain	no	no	yes	no	no
Psychological characteristics					
Fear of the appointment	Very much	Not at all	Very much	Very much	A little
Expected outcome	Very good	Very good	Very good	Good	Good
Systemic health characteristics					
Smoking	no	no	no	yes	past
Diabetes	no	no	no	no	no

SIP – symptomatic irreversible pulpitis; SAP – symptomatic apical periodontitis; Endo – endodontist; GP – general dental practitioner; X- missing data.

Table 2. Pain intensity scores at baseline and each follow-up in patients with persistent pain determined at 6 months following RCT

Pain Intensity (0-10/10)	Total 27 patients	No Pain 22 patients	Pain 5 patients
Pre-operative			
At present			
mean	2.703	2.318	4.4
median	2	1.5	4
range	0-9	0-6	0-9
Average			
mean	4.7	4.3	6.2
median	5	5	6
range	0-10	0-10	3-9
At worst			
mean	6.1	5.7	8
median	8	6.5	8
range	0-10	0-10	6-9
Immediate post-operative			
mean	0.6	0.7	0
median	0	0	0
range	0-3	0-3	0
1 week after RCT			
At present			
mean	1.292	1.158[1]	1.8
median	0	0	2
range	0-7	0-7	0-4
Average			
mean	2.5	2.1	3.8
median	2.5	2	4
range	0-7	0-6	0-7
At worst			
mean	4.3	3.9	5.6
median	5	4	6
range	0-10	0-10	0-10
3 months after RCT			
At present			
mean	1	0.8	2[2]
median	0	0	1.5
range	0-5	0-4	0-5
6 months after RCT			
At present			
mean	1.63	1.364	2.8
median	1	1	3
range	0-6	0-6	1-6
Average			
mean	3	2.7	4.4*
median	4	2	4
range	1-7	1-7	3-6

At worst			
mean	4.4	4	6.4*
median	6	3	6
range	1-10	1-10	4-9
3 years after RCT			
At present			
mean	0.37	0.182	1.2*
median	0	0	1
range	0-4	0-4	0-4
Average			
mean	0.9	0.05	4.6*
median	0	0	4
range	0-7	0-1	2-7
At worst			
mean	1.2	0.5	4.6*
median	0	0	4
range	0-6	0-1	4-6

* - unadjusted $p \leq 0.05$

[1] 3 non-pain patients are missing data

[2] 1 pain patient is missing data

Table 3. Pain duration at baseline and each follow-up in patients with persistent pain determined at 6 months following RCT

Pain Duration	**Total 27 patients**	**No Pain 22 patients**	**Pain 5 patients**
Pre-operative, days in the preceding week			
mean	4.9	4.4	6.8*
median	6	5	7
range	0-7	0-7	6-7
Persistent pain[1], # (%)	6 (22)	5 (22)[2]	1 (20)
1 week after RCT, days in the past week			
mean	3.1	3.1[3]	3.4
median	3	2.5	5
range	0-7	0-7	0-7
3 months after RCT			
Persistent pain[1], # (%)	4 (15)	2 (9)	2 (40)[4]
6 months after RCT, days in the past month			
mean	9.6	8.8	13
median	4	4	10
range	1-30	1-30	2-30
Persistent pain[1], # (%)	9 (33)	7 (32)	2 (40)
3 years after RCT, days in the past month			
mean	1.3	0.2	6.4
median	0	0	3
range	0-20	0-4	2-10

* Unadjusted $p < 0.05$

[1] Tooth pain present at least 8 hours a day, 15 days or more a month, over the last 3 or more months

[2] 1 non-pain patient is missing data

[3] 4 non-pain patients are missing data

[4] 1 pain patient is missing data

Table 4. Interference of pain with usual activities and work.

Pain Interference	**Total 27 patients**	**No Pain 22 patients**	**Pain 5 patients**
Days kept from usual activities in the week prior RCT, mean	0.667	0.636	0.8
median	0	0	0
range	0-3	0-3	0-2
Interference with work in the week prior RCT, # (%)	14 (52)	11[1] (50)	3 (60)
level (0-10/10), mean[2]	3	3.364	1.667
Days kept from usual activities in the 1st week after RCT, mean	1.25	1[3]	2.2
median	0	0	1
range	0-7	0-6	0-7
Interference with work in the 1st week after RCT, # (%)	8 (30)	6[3] (27)	2 (40)
level (0-10/10), mean[2]	1.625	1.5	2
Days kept from usual activities within last month at 6 months after RCT, mean	0.519	0.364	1.2*
median	0	0	0
range	0-8	0-8	0-4
Interference with work within last month at 6 months after RCT, # (%)	5 (19)	3 (14)	2 (40)
level (0-10/10), mean[2]	2.4	2	3
Days kept from usual activities within last month at 3 years after RCT, mean	0.037	0	0.2
median	0	0	0
range	0-1	0	0-1
Interference with work within last month at 3 years after RCT, # (%)	1 (4%)	0 (0)	1 (20)
level (0-10/10), mean[2]	1	0	1

* unadjusted $p < 0.05$

[1] 1 non-pain patient is missing data

[2] not accounting "0/10" responses

[3] 3 non-pain patients are missing data

Table 5. Medications taken to address the pain associated with RCT-treated tooth.

Medications taken for pain	**Total 27 patients**	**No Pain 22 patients**	**Pain 5 patients**
Pain medications taken in the week preceding RCT, # (%)	17 (63)	13 (59)	4 (80)
Pain medications taken in the 1st week after RCT, # (%)	15 (56)	12 (55)[1]	3 (60)
Additional medications within 3 months after RCT, # total (%)	8 (30)	5 (23)	3 (60)
Pain Medications, # (%)	7 (26)	5 (23)	2 (40)
Antibiotics, # (%)	2 (7)	0 (0)	2 (40)*
Additional medications between 3-6 months after RCT, # total (%)	14 (52)	10 (45)	4 (80)
Pain Medications, # (%)	14 (52)	10 (45)	4 (80)
Antibiotics, # (%)	3 (11)	2 (9)	1 (20)
Additional medications between 6 months and 3 years after RCT, # total (%)	7 (26)	4 (18)	3 (60)
Pain Medications, # (%)	7 (26)	4(18)	3 (60)
Antibiotics, # (%)	1 (4)	0 (0)	1 (20)

* unadjusted $p < 0.05$

[1] 4 non-pain patients missing data

Table 6. Health care utilizations by patients with persistent pain at 6 months between 0 months to >3 years following initial RCT

Health Care Utilization	**Total 27 patients**	**No Pain 22 patients**	**Pain 5 patients**	notes
Additional treatment between 0-3 months after RCT, total	***4 (15%)***	***3 (14%)***	***1 (20%)****	
Re-treatment	1 (4%)	1 (5%)	0 (0%)	1 appt
Extraction	0 (0%)	0 (0%)	0 (0%)	
Occlusal adjustments	1 (4%)	0 (0%)	1 (20%)	3 appt.; 2 appt. for x-rays
Medical doctor visits	2 (7%)	2 (9%)	0 (0%)	3 appt
Additional treatment between 3-6 months after RCT, total	***5 (19%)***	***3 (14%)***	***2 (40%)***	
Re-treatment	2 (7%)	1 (5%)	1 (20%)	5 appt.; 9 appt. for x-rays
Extraction	1 (0%)	0 (0%)	1 (20%)	1 appt.
Unspecified dental treatment	1 (4%)	1 (5%)	0 (0%)	1 appt.
Medical doctor visits	2 (7%)	2 (9%)	0 (0%)	2 appt.
Chiropractic care	1 (4%)	1 (5%)	0 (0%)	4 appt.
Additional treatment between 6 months and 3 years after RCT, total	***5 (19%)***	***4 (18%)***	***1 (20%)***	14 DDS appt.
Re-treatment	3 (11%)	2 (9%)	1 (20%)	
Extraction	1 (4%)	1 (5%)	0 (0%)	
Crown replacement	1 (4%)	1 (5%)	0 (0%)	
Medical doctor visits	1 (4%)	1 (5%)	0 (0%)	3 appt.
Total additional treatment between 0 months and 3 years after RCT	***11 (41%)***	***7 (32%)***	***4 (80%)***	36 DDS appt
Re-treatments	6 (22%)	4 (18%)	2 (40%)	
Extractions	2 (7%)	1 (5%)	1 (20%)	
Other dental treatments	2 (7%)	1 (5%)	1 (20%)	
Medical doctor visits	3 (11%)	3 (14%)	0 (0%)	8 appt.
Chiropractic care	1 (4%)	1 (5%)	0 (0%)	4 appt.

* 1 pain patient is missing data

Appt. – appointment(s), DDS – dentist/dental.

Table 7. Additional care sought to manage pain associated with the tooth that received RCT since 6-month follow-up.

Additional care sought to manage pain since 6-month follow-up	**Total** 27 patients	**No pain** 22 patients	**Pain** 5 patients
Additional care since 6-month follow up:	8 (30%)	6 (27%)	2 (40%)
Dental treatments:	5 (19%)	4 (18%)	1 (20%)
Appointments with a DDS	14	8	6
Additional x rays	5 (19%)	3 (14%)	2 (40%)
Extraction of the tooth	1 (4%)	1 (5%)	0 (0%)
Additional root canal treatments	3 (11%)	2 (9%)	1 (20%)
Crown replacement	1 (4%)	1 (5%)	0 (0%)
Medical treatments	1 (4%)	1 (5%)	0 (0%)
Appointments with an MD	3	3	0
Pain medications in the past month	7 (26%)	4 (18%)	3 (60%)
Medications since 6-month follow-up:			
Pain medications	7 (26%)	4 (18%)	3 (60%)
Antibiotics	1 (4%)	0 (0%)	1 (20%)*

* - unadjusted $p \leq 0.05$

Table 8. Characteristics of pain experienced at >3 years after RCT

Pain characteristics at >3-year follow-up	**Total** 27 patients	**No pain** 22 patients	**Pain** 5 patients
Days in the past month experiencing pain, median (range)	0 (0-20)	0 (0-4)	3 (2-20)*
Pain intensity at the visit, median (range)	0 (0-4)	0 (0-4)	1 (0-4)*
Average pain intensity in the past month median (range)	0 (0-7)	0 (0-1)	4 (2-7)*
Worst pain intensity in the last month median (range)	0 (0-4)	0 (0-5)	4 (4-6)*
Days kept from usual activities median (range)	0 (0-1)	0 (0)	0 (0-1)*
Pain interfered with ability to work	1 (4%)	0 (0%)	1 (20%)*

* - unadjusted $p \leq 0.05$

Table 9. Patient-related characteristics

Patient-related characteristics	**Total 27 patients**	**No Pain 22 patients**	**Pain 5 patients**
Female gender, # (%)	17 (63)	13 (59)[1]	4 (80)
Age, mean	45.58	45.57[1]	45.6
median	51	52	49
range	19-66	19-63	26-66
Income > $50,000, # (%)	14 (52)	9 (41)[1]	5 (100)
Completed higher or advanced education, # (%)	17 (63)	13 (59)	4 (80)
Widespread pain, # (%)	7 (26)	6 (27)[1]	1 (20)
Very much fearful about RCT, # (%)	6 (22)	3 (14)	3 (60)*
Optimism about the outcome, # (%)	26 (96)	21 (95)	5 (100)

* unadjusted p = 0.0537

[1] 1 non-pain patient is missing data

Table 10. Dentist-related characteristics.

Dentist-related characteristics	**Total 27 patients**	**No Pain 22 patients**	**Pain 5 patients**
General practitioner, # (%)	12 (44)	10 (45)	2 (40)
Endodontist, # (%)	15 (56)	12 (55)	3 (60)
Pre-emptive analgesia / intraoperative sedation, # total (%)	6 (22)	4 (18)	2 (40)
benzodiazepine	1 (4)	1 (5)	0 (0)
NSAID/Acetaminophen	1 (4)	1 (5)	0 (0)
N_2O sedation	5 (19)	3 (17)	2 (40)
Local anesthesia failure, # (%)	5 (19)	5 (23)	0[1] (0)
Additional local anesthetic injection, # (%)	10 (37)	8 (36)	2 (40)
Misadventures, # (%)	2 (7)	2 (9)	0 (0)
perforation	0	0	0
non-negotiable	1 (4)	1 (5)	0 (0)
file separation	0	0	0
inadvertent filling	1 (4)	1 (5)	0 (0)
Obturation in 1 visit, # (%)	25 (93)	21 (95)	4 (80)
Permanent restoration in the access, # (%)	11 (41)	9 (41)[2]	2 (40)
Difficulty performing RCT, # (%)	6 (22)	6 (27)	0 (0)
DDS perceived likelihood of pain at 6 months after RCT, # (%)			
none (<0.1%)	14 (52)	11 (50)	3 (60)
slight (0-1%)	10 (37)	8 (36)	2 (40)
moderate (1-5%)	3 (11)	3 (14)	0 (0)
high (>5%)	0	0	0

[1] 1 pain patient reported that anesthesia was insufficient

[2] 1 non-pain patient is missing data

Table 11. Tooth-related characteristics.

Tooth-related characteristics	**Total 27**	**No Pain 22**	**Pain 5**
Maxillary tooth, total # (%)	17 (63)	15 (68)	2 (40)
anterior, # (%)	4 (15)	4 (18)	0 (0)
posterior, # (%)	13 (48)	11 (50)	2 (40)
Mandibular tooth, total # (%)	10 (37)	7 (32)	3 (60)
anterior, #	0	0	0
posterior, # (%)	10 (37)	7 (32)	3 (60)
Diagnosis			
Pulpal, # (%)			
Normal/reversible/AIP	3 (11)	3 (14)	0 (0)
Necrotic	14 (52)	13 (59)	1 (20)
SIP	10 (37)	6 (27)	4 (80)
Apical, # (%)			
Normal	7 (26)	6 (27)	1 (20)
SAP	10 (37)	6 (27)	4 (80)
AAP	6 (22)	6 (27)	0 (0)
AAA	2 (7)	2 (9)	0 (0)
CAA	2 (7)	2 (9)	0 (0)

AIP – asymptomatic irreversible pulpitis; SIP – symptomatic irreversible pulpitis; SAP – symptomatic apical periodontitis; AAP – asymptomatic apical periodontitis; AAA – acute apical abscess; CAA – chronic apical abscess.

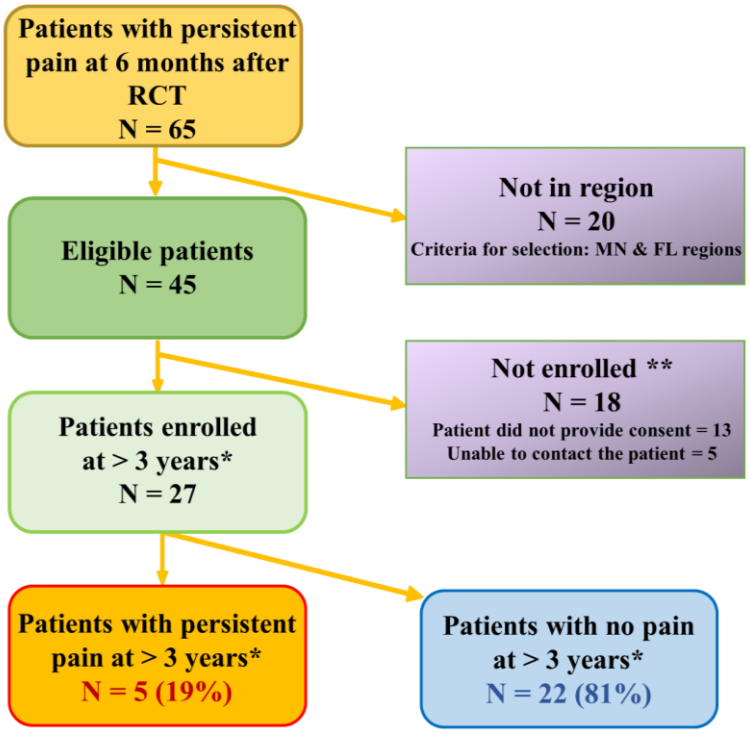
Table 12. Pain quality-related characteristics.

Pain-related characteristics	**Total 27 patients**	**No Pain 22 patients**	**Pain 5 patients**
Quality, # (%)[1]			
Dull	8 (30)	8 (36)	0 (0)
Sharp	8 (30)	7 (32)	1 (20)
Aching	12 (44)	9 (41)	3 (60)
Throbbing	13 (48)	9 (41)	4 (80)
Burning	1 (4)	1 (5)	0 (0)
Shooting	2 (7)	1 (5)	1 (20)
Electric	3 (11)	3 (14)	0 (0)
Spontaneity, # (%)			
Spontaneous	15 (56)	12 (55)	3 (60)
Provoked	16 (59)	14 (64)	2 (40)

[1] 1 non-pain patient is missing data

Figures

Figure 1. Flow diagram describing the disposition of consecutive eligible patients.



* Mean (±SD) time since the initial RCT: 3.4±0.2 years (range: 3.1–3.9)
** The 18 patients not enrolled were found to be similar in patient-, tooth-, and pain-related characteristics at baseline and at the 6-month follow-up to those who were enrolled (Table 1 and 2 in Appendix).

Figure 2. Mean pain intensity on average across all time points among patients with persistent pain at >3 years.

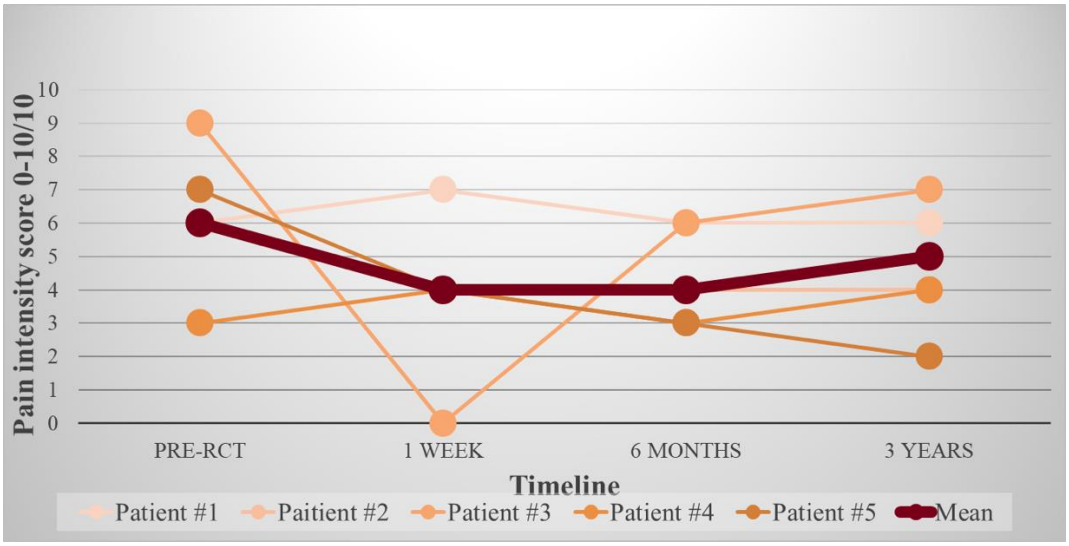


Figure 3. Proportion of patients who report persistent pain at 6 months after RCT receiving additional healthcare in each time interval over the >3-year time period.

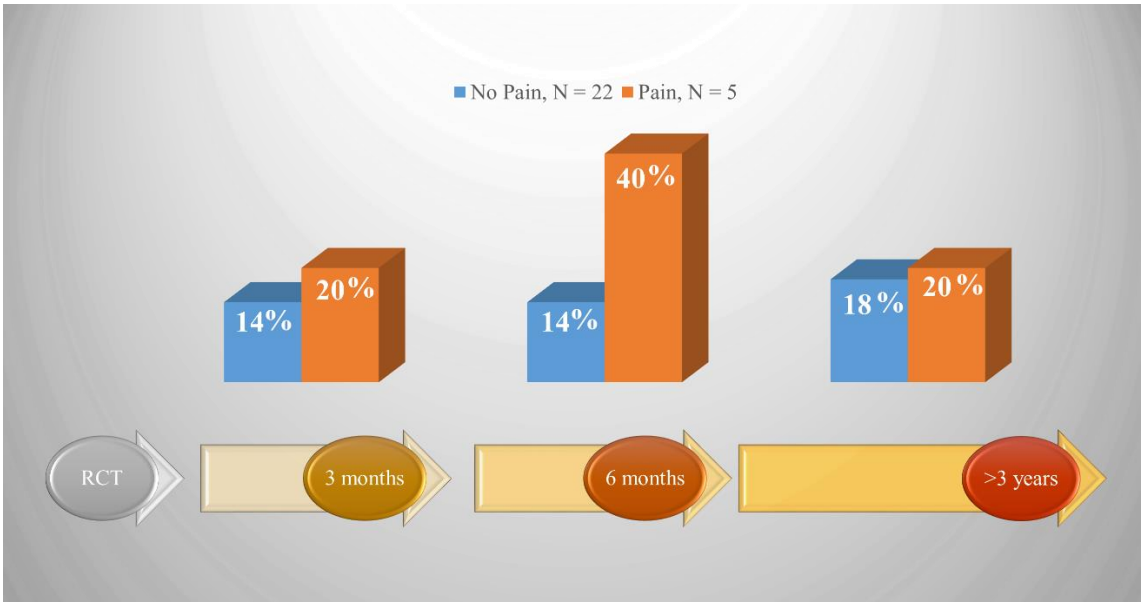


Figure 4. Cumulative proportion of patients who report persistent pain at 6 months after RCT receiving additional care over the >3-year time frame.

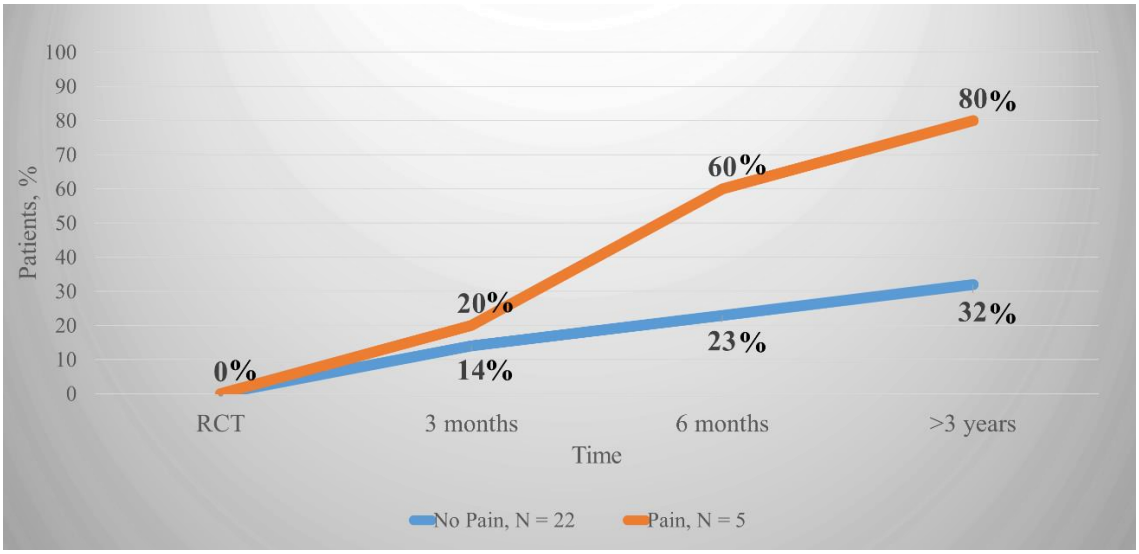
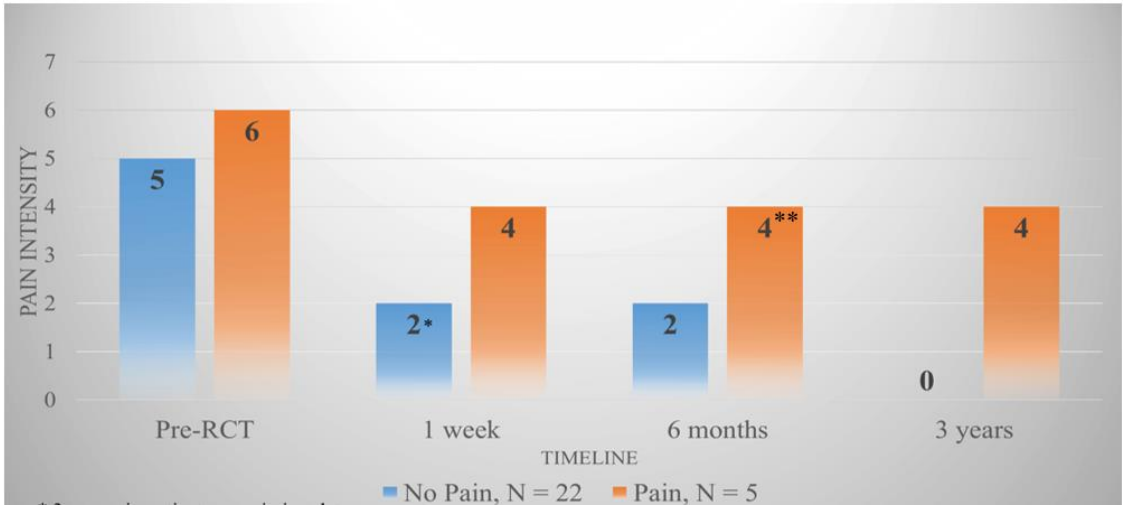


Figure 5. Median pain intensity on average 0-10/10 among patients with persistent pain at 6 months post-RCT across all time points.



* 3 non-pain patients are missing data
** $p = 0.0452$

Figure 6. Possible associations with the chronification of the persistent pain measured at 6 months post-RCT.

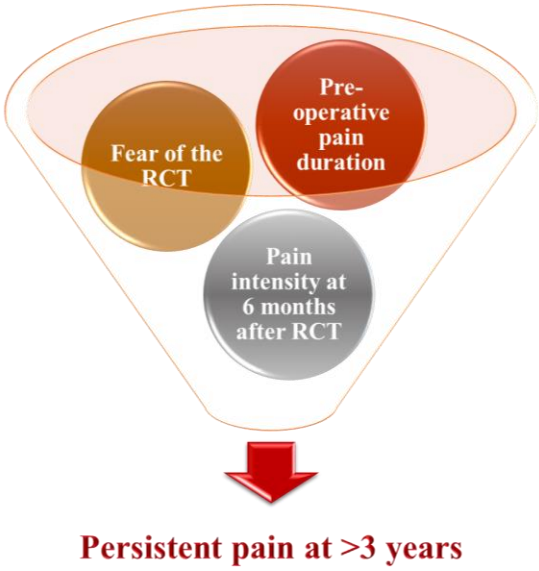
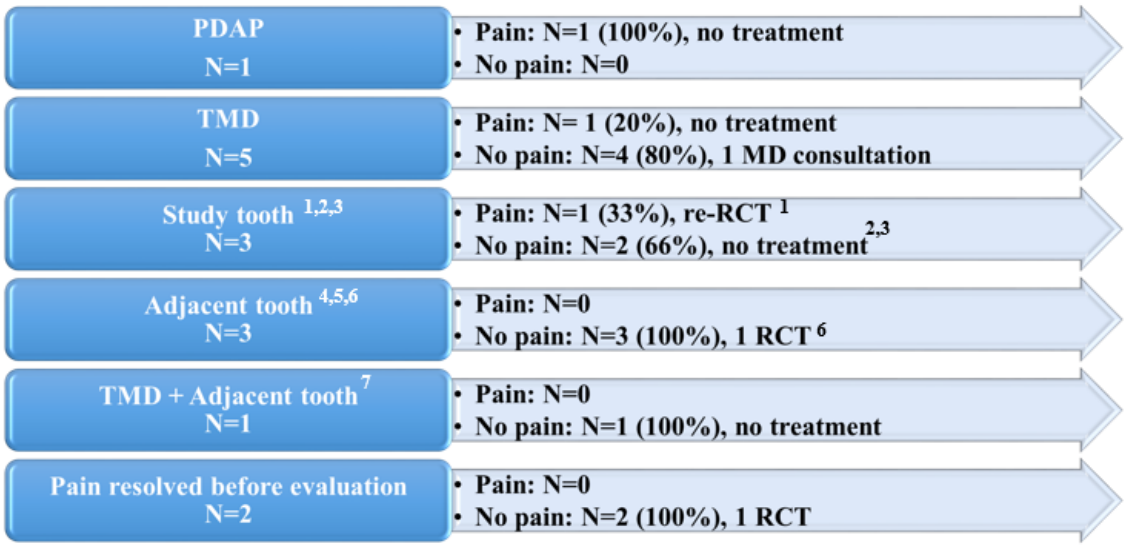


Figure 7. Differential diagnoses for the persistent pain given at 6-months following the initial RCT (on the left) with their pain outcomes at >3 years and additional care since the diagnosis (on the right).



Diagnoses for odontogenic pain:

1. SAP (missed MB2)
2. SAP (C-shaped canal)
3. SAP (missed MB2)
4. SAP (calcified and curved MB2)
5. SAP (missed canal)
6. SIP
7. SAP (underfilled)

* 15 patients who had a consensus diagnosis for the persistent pain at 6-months after RCT represented 56% of the sample in this 3-year outcome study

** 11 (85%) out of 13 examined patients had TMD and/or headache either as co-morbid unrelated diagnoses (6, 46%) or the causes (6, 46%) of the persistent tooth pain

*** 9/10 non-pain patients and 1/3 pain patients had other chronic pain conditions

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Appendices

Table 1. Baseline characteristics of the followed vs. not followed subjects at the initiation of the study.

Baseline characteristics at the initiation of the study	Persistent pain in 6 months N = 45	Not followed subjects N = 18	Followed subjects N = 27
Patient-related characteristics: N [% (95%CI)]			
Mean age in years	44.5 (40.4-48.6)	42.9 (37.3-48.5)	45.6 (39.9-51.3)
Number missing	1	0	1
Female gender	33 [0.73 (0.06-0.86)]	16 [0.89 (0.74-1)]	17 [0.63 (0.45-0.81)]
Number missing	1	0	1
Race or ethnicity			
Non-Hispanic white	42 [0.93 (0.86-1)]	17 [0.94 (0.84-1)]	25 [0.93 (0.83-1)]
Other	3 [0.07 (0-0.14)]	1 [0.06 (0-0.16)]	2 [0.07 (0-0.17)]
Number missing	0	0	0
Highest level of education completed			
Less than college degree	17 [0.38 (0.24-0.52)]	7 [0.39 (0.16-0.61)]	10 [0.37 (0.19-0.55)]
College degree or more advanced	28 [0.62 (0.48-0.76)]	11 [0.61 (0.39-0.84)]	17 [0.63 (0.45-0.81)]
Number missing	0	0	0
Tooth-related characteristics: N [% (95%CI)]			
Maxillary tooth	28 [0.62 (0.48-0.76)]	11 [0.61 (0.39-0.84)]	17 [0.63 (0.45-0.81)]
Number missing	0	0	0
Posterior tooth	37 [0.82 (0.71-0.93)]	15 [0.83 (0.66-1)]	22 [0.81 (0.67-0.96)]
Molar	28 [0.62 (0.48-0.76)]	13 [0.72 (0.52-0.93)]	15 [0.56 (0.37-0.74)]
Premolar	9 [0.20 (0.08-0.32)]	2 [0.11 (0-0.26)]	7 [0.26 (0.09-0.43)]
Number missing	0	0	0
Pulpal endodontic diagnoses			
Necrotic pulp	22 [0.49 (0.34-0.64)]	8 [0.44 (0.22-0.67)]	14 [0.52 (0.33-0.71)
Normal pulp or reversible pulpitis	5 [0.11 (0.02-0.20)]	2 [0.11 (0-0.26)]	3 [0.11 (0-0.23)]
Irreversible pulpitis	18 [0.40 (0.26-0.54)]	8 [0.44 (0.22-0.67)]	10 [0.37 (0.19-0.55)]
Number missing	0	0	0
Apical endodontic diagnoses			
Normal apical tissues	8 [0.18 (0.07-0.29)]	1 [0.06 (0-0.16)]	7 [0.26 (0.09-0.43)]
Symptomatic apical periodontitis	21 [0.47 (0.32-0.61)]	11 [0.61 (0.39-0.84)]	10 [0.37 (0.19-0.55)]
Asymptomatic apical periodontitis	12 [0.27 (0.14-0.40)]	6 [0.33 (0.12-0.55)]	6 [0.22 (0.07-0.38)]
Acute apical abscess	2 [0.04 (0-0.11)]	0 [(0)]	2 [0.07 (0.07-0.17)]
Chronic apical abscess	2 [0.04 (0-0.11)]	0 [(0)]	2 [0.07 (0.07-0.17)]
Number missing	0	0	2
Tooth and other pain-related characteristics: N [% (95%CI)]			
Number of days experiencing pain in the past week	4.8 (4.0-5.6)	4.8 (3.5-6.1)	4.9 (3.9-5.9)
Number missing	0	0	0
Pain intensity at the visit	3.0 (2.1-3.9)	3.4 (2.8-5.0)	2.7 (1.6-3.8)
Number missing	0	0	0

Average pain intensity in the past week Number missing	4.6 (3.8-5.4) 0	4.5 (2.9-6.1) 0	4.7 (3.7-5.7) 0
Worst pain intensity in the past week Number missing	6.0 (5.0-7.0) 0	5.9 (4.2-7.6) 0	6.1 (5.0-7.2) 0
Number of patients with persistent pain (>8h/d >15d/mo >3mo) Number missing	11 [0.24 (0.12-0.37)] 1	5 [0.28 (0.07-0.49)] 0	6 [0.22 (0.07-0.38)] 1
Number of patients that took pain medications in the past week Number missing	30 [0.67 (0.53-0.80)] 1	13 [0.72 (0.52-0.93)] 0	17 [0.63 (0.45-0.81)] 1
Number of patients: Currently smoking Number missing Smoking in the past >100 cig. Number missing	 6 [0.13 (0.03-0.23)] 1 20 [0.44 (0.30-0.59)] 1	 2 [0.11 (0-0.26)] 0 7 [0.39 (0.16-0.61)] 0	 4 [0.15 (0.01-0.28)] 1 13 [0.48 (0.29-0.67)] 1
Number of patients with diabetes or high blood sugar Number missing	3 [0.07 (0-0.14)] 2	2 [0.11 (0-0.26)] 0	1 [0.04 (0-0.11)] 2
Number of patients with pain in >1 area of the body at least 4d/wk Number missing	14 [0.31 (0.18-0.45)] 1	7 [0.39 (0.16-0.61)] 0	7 [0.26 (0.09-0.43)] 1

Table 2. Baseline tooth and pain-related characteristics of the followed vs. not followed subjects at the 6-month.

Baseline characteristics at 6 months	Persistent pain in 6 months N = 45	Not followed subjects N = 18	Followed subjects N = 27
Tooth and other pain-related characteristics: N [% (95%CI)]			
Number of days experiencing pain in the past month	8.8 (6.0-11.6)	7.7 (3.7-11.7)	9.6 (5.8-13.4)
Pain intensity at the visit	1.5 (0.9-2.1)	1.3 (0.4-2.2)	1.6 (0.9-2.3)
Average pain intensity in the last month	2.9 (2.3-3.5)	2.8 (1.8-3.8)	3.0 (2.3-3.7)
Worst pain intensity in the past month	4.2 (3.4-5.0)	3.9 (2.8-5.0)	4.4 (3.4-5.4)
Persistent pain (>8h/d >15d/mo >3mo)	12 [0.27 (0.14-0.40)]	3 [0.17 (0-0.34)]	9 [0.33 (0.16-0.51)]
Number of patients that took pain medications in the past month	24 [0.53 (0.39-0.68)]	10 [0.54 (0.33-0.79)]	14 [0.52 (0.33-0.71)]
Number of patients that received additional RCT Number of appointments	5 [0.11 (0.02-0.20)] 8	3 [0.17 (0-0.34)] 3	2 [0.07 (0-0.17)] 5
Number of patients that had their tooth was extracted	2 [0.04 (0-0.11)]	1 [0.06 (0-0.16)]	1 [0.04 (0-0.11)]
Number of patients that had additional x-rays done	10 [0.22 (0.10-0.34)]	3 [0.17 (0-0.34)]	7 [0.26 (0.09-0.43)]
Number of patients that had an appointment with a MD Number of appointments	4 [0.09 (0.01-0.17)] 6	2 [0.11 (0-0.26)] 4	2 [0.07 (0-0.17)] 2